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09/424,498	02/15/2000	HANS-PETER SCHWARZ	BHV-314.01	8060

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EXAMINER	
SCHNIZER, HOLLY G	

ART UNIT	PAPER NUMBER
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21

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application No. 09/424,498	Applicant(s) SCHWARZ ET AL.	
	Examiner Holly Schnizer	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31,32,35-37,39-41 and 43-73* is/are pending in the application.

4a) Of the above claim(s) *45-63* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31,32,35-37,39,40,43,44 and 64-73* is/are rejected.

7)☒ Claim(s) *41* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 February 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *20* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 4, 2002 has been entered.

Status of the Claims

In the Amendment filed December 4, 2002, Claims 72-73 were added. Therefore, Claims 31, 32, 35-37, 39-41, and 43-73 are pending, Claims 45-63 are withdrawn as directed to a non-elected invention, and Claims 31, 32, 35-37, 39-41, 43-44, and 64-73 have been considered in this Office Action.

Withdrawal of Objections

The objection of Claim 45 is withdrawn in light of Applicants arguments.

Rejections Withdrawn

The rejection of Claim 32 under 35 U.S.C. 112, second paragraph for the recitation of "essentially comprised of" is withdrawn in light of the amendment to the claim.

The rejection of Claims 31-32, 39-40, 43-44, and 64-66 under 35 U.S.C. 102(b) as being anticipated by Takagi et al. (J. Biol. Chem. (1989) 264(11): 6017-1020; ref. AY of IDS of Paper No. 6) is withdrawn in light of the amendment to Claim 31 and Applicants arguments.

The rejection of Claims 31, 32, 35, 36, 37, 39, 40, 43, 44, and 64-71 under 35 U.S.C. 103(a) as being unpatentable over Leyte et al. (Biochem. J. (1991) 274: 257-261; ref. AW in IDS of Paper No. 6) and Takagi et al. (J. Biol. Chem. (1989) 264(11): 6017-1020; ref. AY of IDS of Paper No. 6) in view of Burnouf-Radosevich et al. (U.S. Patent No. 5,408,039, 1995) and Wise et al. (Cell (1988) 52: 229-236) is withdrawn in light of Applicants arguments. The examiners motivation to make a pharmaceutical composition comprising the vWF propeptide or pro-vWF was based on the teaching that the propeptide is essential to forming large mulitmers, the absence of which are associated with disease. However, Applicants point out that the propeptide and the mature vWF do not associate in circulation. Therefore, from the prior art of record, it appears one of ordinary skill in the art at the time of the invention would not have expected that administering the propeptide would result in the increase in large multimers in circulation.

The rejection of Claim 41 under 35 U.S.C. 103(a) as being unpatentable over Leyte et al. (Biochem. J. (1991) 274: 257-261; ref. AW in IDS of Paper No. 6),Takagi et al. (J. Biol. Chem. (1989) 264(11): 6017-1020; ref. AY of IDS of Paper No. 6), and Burnouf-Radosevich et al. (U.S. Patent No. 5,408,039, 1995) as applied to claims 31, 32, 35, 36, 37, 39, 40, 43, 44, and 64-71 above, and further in view of Kaufman (U.S.

Patent No. 5,198,349, 1993) is withdrawn for the same reasons given above for the withdrawal of the obviousness rejection over Leyte et al., Takagi et al., Burnouf-Radosevich et al. and Wise et al.

Rejections Maintained

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 31-32, 35-37, 39-40, 43-44, 66-69 and new Claims 72 and 73 are rejected under 35 U.S.C. 102(b) as being anticipated by Burnouf-Radosevich et al. (U.S. Patent No. 5,408,039, 1995). It is noted that the references of Turecek et al., Ruggeri et al., and Wise et al. are used as evidence for inherent properties of the preparation of Burnouf-Radosevich et al. in response to Applicants arguments. However, the Burnouf-Radosevich et al. reference alone meets all of the limitations of the claims.

A response to Applicant's arguments is provided after the following review of the Burnouf-Radosevich et al. teachings as stated in the previous Office Action. Burnouf-Radosevich et al. teach that pharmaceutical compositions comprising vWF from vWF-enriched plasma derivatives are very well known in the art (Col. 1-Col. 2). Burnouf-Radosevich et al. disclose a highly purified vWF concentrate that is subjected to a

solvent-detergent treatment known for its efficiency in destroying lipid-enveloped viruses (Col. 5, Example and "Viral Inactivation Treatment"). The vWF is synthesized as a pre-pro-peptide. Upon cleavage of the signal peptide, the pro-vWF (containing the propeptide and mature peptide segments) dimerizes, assembles into multimers, and then the propolypeptide (741 aa segment) is removed by proteolytic cleavage. However, cleavage is not always complete. Therefore, it appears that a vWF plasma derivative, such as disclosed in Burnouf-Radosevich et al. would comprise the vWF pro polypeptide, the pro-vWF, as well as the mature vWF. In addition, Burnouf-Radosevich et al. teach that the composition disclosed therein may also comprise Factor VIII (Col. 5, lines 55-60). Therefore, the claims appear to be anticipated by Burnouf-Radosevich et al.

Claim 67 (composition comprising the pro-vWF) is also rejected for the same reasons applied above. Claim 68 is rejected because the fact that pro-vWF is recombinant does not patentably distinguish the composition over that of the prior art since both recombinant and isolated forms of pro-vWF would have the same sequence, structure, and function. Claim 69 is rejected for the reasons stated above. It is known that the propeptide (741 aa segment) is required for factor VIII binding either as part of the pro-vWF or in trans as the propeptide. Thus, since Burnouf-Radosevich et al. teach that the composition may also comprise Factor VIII (Col. 5, lines 55-60) and since this composition maintains Factor VIII and vWF activity (see Col. 5, lines 64-66), it would be inherent that the pro-vWF complexed to the factor VIII.

Claims 72 and 73 add the limitation that the compositions are formulated for parenteral administration. Such limitation amounts to intended use and the preparations of Claims 72 and 73 do not appear to contain any components not taught in the Burnouf-Radosevich et al. and thus do not patentably distinguish the claimed composition over the prior art.

Applicants refer to statements made in Turecek et al. (Histochem. Cell Biol. (2002) 117: 123-129; cited in IDS), Varadi et al. (Thromb. Haemost. (2001) 86: 1449-1458) and Borchiellini (Blood (1996) 88: 2951-2968; cited in IDS) to support their argument that plasma contains low to undetectable levels of pro-vWF and the propeptide. This argument has been considered but is not deemed persuasive for the following reasons. First, Fujisawa et al. (Eur. J. Biochem. (1991) 196: 673-677 at p. 673, Col. 1, lines 8-10; cited in IDS) states that the propolypeptide of vWF (pp-vWF) is present in plasma, endothelial cells, and platelets (see pl. 673, Col. 1, lines 8-10) and Ruggeri et al. states "a certain proportion of normal plasma vWf multimers contain pro-vWf peptide (p. 594, Col. 2, lines 16-18). Thus, it appears that the literature indicates that these proteins are contained in the plasma. Second, Applicants argument only indicates that there is low or trace amounts of the pro-vWf and pp-vWF present in plasma. The claims are drawn to preparations comprising pro-vWF and pp-vWF and does not specify a certain concentration, thus the presence of any amount of the pro-vWF or pp-vWF peptides, whether trace or abundant, in the Burnouf-Radosevich et al. reference is sufficient to meet the limitations of the claims. The examiner notes that

Claims 64 and 65 wherein the peptide is 90% and 95% pure was not included in the rejection.

The vWF propeptide would be present in the Burnouf-Radosevich et al. preparation regardless of whether or not it is associated with mature vWF.

Applicants argue that there is no evidence that pro-vWF or vWF propeptide would remain in solution following centrifugation and aluminum hydroxide purification steps which precede formation of the Burnouf- Radosevich et al. composition. Applicants' argument that the propeptide is separated from the mature vWF upon secretion is convincing. However, regardless of whether or not the propeptide associates with the mature vWF and absent evidence to the contrary, the preparation of the Burnouf-Radosevich et al. composition does not contain a step that would separate the propeptide from the mature vWF. The protein of Burnouf-Radosevich et al. only uses anion exchange chromatography in the purification process. The propeptide sequence is highly homologous to that of the mature vWF. Therefore, separation by charge would not be sufficient to separate the propeptide from the mature form of the protein. This is supported by the fact that there are no reports of purifying the propeptide using anion exchange. Rather, the well-known purification procedures for the propeptide are by size exclusion or affinity chromatography to ensure that the propeptide is separated from the mature vWF. For example, the Specification states that the propeptide may be separated from the mature vWF by size (gel filtration) (p. 5 first paragraph). Moreover, Takagi et al. emphasizes that the propeptide was purified by three different affinity chromatographies (see p. 6018, Col. 1, first paragraph). In

addition, Borchiellini et al. (Blood (1996): 88(8): 2951-2958; cited in IDS) teach that the propeptide composition describe therein was passed through a column containing a monoclonal antibody specific for the mature vWF in order to remove the pro-vWF and mature vWF from the propeptide (p. 2952, Col. 2, 2nd paragraph). Finally, even in instances wherein immuno-affinity chromatography (using antibodies specific for the mature vWF) is used to try to separate the propeptide from pro-vWF/mature vWF solutions, minute amounts of the propeptide are still present in the purified mature vWF compositions (see Turecek et al. Blood (1999) 94(5): 1637-1647, especially p. 1638, Col. 1, 2nd para. from bottom; previously cited in Paper No. 16). Thus, absent any evidence that the Burnouf-Radosevich et al. method involves a step to specifically eliminate the propeptide from the composition isolated therein, it appears that the Burnouf-Radosevich et al. preparation contains the vWF propeptide.

Pro-vWF would be present in the Burnouf-Radosevich et al. preparation

With respect to pro-vWF, Applicants again argue that it would be rapidly degraded. This argument has been considered but is not deemed persuasive because Applicants have not addressed the evidence that pro-vWF is present circulating in vivo. As stated in the previous Office Action, Wise et al. indicate that pro-vWF cleavage is not required for secretion or multimer formation. Wise et al. state that multimers can be assembled from uncleaved pro-vWF and that uncleaved pro-vWF are present in multimers from endothelial cell culture medium and circulating in vivo (p. 231, section bridging Col. 1 and 2). Ruggeri et al. (Thromb. Haem. (1992) 67(6) 594-599) also state that a certain proportion of normal plasma vWF multimers contain pro-vWF peptide that

are secreted from endothelial cells by the constitutive pathway (see p. 594, Col. 2, lines 16-20). It is also noted that Wise et al. show that the pro-vWF is readily apparent in the cell culture medium of cells expressing a wild-type pre-pro-vWF (see Fig. 6A).

New Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 31, 32, 39, 40, 43, 44, 64, 65, and 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takagi et al. (J. Biol. Chem. (1989) 264(11): 6017-6020) in

view of EP 0 131 740 (cited in IDS of Paper No. 20), Blann et al. (Eur. J. Vasc. Surg. (1994) 8 : 10-15; cited in IDS) and Applicants admissions in the instant Specification.

Takagi et al. disclose a composition comprising vWF propolypeptide isolated from human platelets (see p, 6017, Experimental Procedures). The purification process of Takagi et al. includes three affinity chromatography steps and the resulting propeptide appears to be at least 95% pure. Since the vWF propolypeptide is a glycoprotein isolated from platelets it is considered a platelet glycoprotein component (clms 39-40). Takagi et al. concludes that pp-vWF has a strong affinity to collagen and that it inhibits collagen-induced aggregation of human platelets and suggests that pp-vWF and vWF may have opposing effects on hemostasis (see abstract). Takagi further concludes that pp-vWF could have a unique function in hemostasis independent of mature vWF, since it is known to be released from platelets upon activation by thrombin, collagen, and ADP. It is stated that since pp-vWF inactivates collagen upon short incubation, released pp-vWF should immediately bind to exposed collagen layer at the site of vessel wall injury and may prevent further adhesion of platelets to subendothelium (seep. 6018, Col. 2, lines 2-10 from bottom).

Takagi et al. do not teach that the purified vWF propolypeptide has been treated for at least one of virus inactivation or virus removal or that the pp-vWF composition is appropriate for therapeutic administration.

EP 0 131 740 teaches a method for making a composition containing blood proteins free of lipid containing viruses.

The purification of pp-vWF is known in the art as evidenced by Takagi et al. as well as admitted by the Specification (p. 4. last paragraph). A wide variety of methods of treating compositions for virus removal or inactivation are very well known in the art (see Specification, p. 7, first paragraph; or EP 0 131 740, cited in IDS of Paper No. 20).Therefore, making a composition identical to that of the present invention was well within the skill of the art at the time of the invention and one only needs motivation to treat the composition of Takagi et al. for viral removal or inactivation. This motivation is found in the combined teachings of Takagi et al. and Blann et al.

Blann et al. teaches (as noted by the Specification as originally filed, p. 3, paragraph 3) that vWF levels are increased with risk factors for atherosclerosis and in patients with diffuse arterial disease (p. 13, Col. 2, lines 1-3). Blann et al. also suggests that future therapeutic strategies could involve agents that oppose vWF (p. 13, Col. 2, last paragraph). One disadvantage associated with coagulation promoting preparations is the risk of arterial thrombosis. Takagi et al. suggests that pp-vWF inhibits the collagen-induced platelet aggregation and has an opposite effect on platelet adhesion. Thus, it would have been obvious to one of ordinary skill in the art at the time of the invention, to purify the propeptide by modifying the method of Takagi et al. to include a step of virus removal or inactivation as taught in EP 0 131 740. One of ordinary skill would have had a reasonable expectation of success in using such a composition since Takagi et al. teaches that the propeptide activity opposes that of the mature vWF and Blann et al. describe a need in the art for preparations that would

oppose the high vWF levels and activity that are associated with atherosclerosis and arterial disease. Thus, the claims are unpatentable over the prior art.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 70 and 71 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. A 90% or 95% pure pro-vWF composition, critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976).

The instant specification does not specifically provide a method of purification of pro-vWF but only refers to Fischer et al. (FEBS Letters 351, 345-348 (1994)) or Borchiellini et al. (Blood 88(8) 1996, 2951-2958) for instruction as to how to purify pro-vWF and the propeptide. However, while Fischer et al. and Borchiellini et al. teach the expression of pro-vWF, the examiner did not find a protocol for the purification of pro-vWF specifically. A search of the prior art also did not reveal any prior art references teaching how to make a composition comprising pro-vWF wherein the pro-vWF is at least 90% or 95% pure. The closest reference found to obtaining such a composition was Turecek et al. (Blood (1999) 94(5): 1637-1647) and Varadi et al. (Thromb. Haemost. (2001) 86: 1449-1458; cited in IDS of Paper No. 20) which were published

after the filing date of the present application. Turecek et al. teach purification of the pro-vWf by immuno-affinity chromatography using an antibody to the mature vWF (p. 1638, second paragraph from bottom) resulting in a composition comprising pro-vWF that was 50% pure at best (see p. 1640, Col. 1, Results). Likewise, the pro-vWF described in Varadi et al. is less than 50% pure (they report equal amounts of mature and pro-vWF and less than 2% pp-vWF; see para. bridging p. 1449-1450). Since Applicants state that the pro-vWF is highly labile (see Paper No. 19, p. 5) and since there is no evidence of art prior to the invention that teaches the purification of pro-vWF, such a teaching is required to support the claims to pro-vWF compositions wherein the pro-vWF protein is 90% or 95% pure.

Claim Objections

Claim 41 is objected to for depending from a rejected claim but would be allowable if rewritten in independent form including all of the limitations of the claim from which it depends.

Conclusions

No Claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (703) 305-3722. The examiner can normally be reached on Monday through Wednesday from 8 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703 308-0196.

Holly Schnizer
April 2, 2003

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